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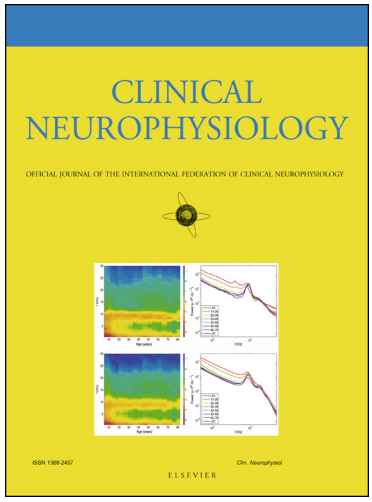

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Posterior Alpha Oscillations Reflect Attentional Problems in Boys with Attention Deficit Hyperactivity Disorder

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Highlights

- Typically developing boys showed adult-like hemispheric alpha lateralization.
- Boys with ADHD lacked hemispheric alpha lateralization during attention allocation.
- Alpha lateralization was significantly stronger in controls than in boys with ADHD.

Abstract

Objective

This study aimed to characterize alpha modulations in children with ADHD in relation to their attentional performance.

Methods

The posterior alpha activity (8-12 Hz) was measured in 30 typically developing children and 30 children with ADHD aged 7-10 years, using EEG while they performed a visuospatial covert attention task. We focused the analyses on typically developing boys (N=9) and boys with ADHD (N=17).

Results

Alpha activity in typically developing boys was similar to previous results of healthy adults: it decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. However, in boys with ADHD this hemispheric lateralization in the alpha band was not obvious (group contrast, $p = .018$). A robust relation with behavioral performance was lacking in both groups.

Conclusions

The ability to modulate alpha oscillations in visual regions with the allocation of spatial attention was clearly present in typically developing boys, but not in boys with ADHD.

Significance

These results open up the possibility to further study the underlying mechanisms of ADHD by examining how differences in the fronto-striatal network might explain different abilities in modulating the alpha band activity.

Keywords

Alpha inhibition, covert attention, children, electroencephalography, ADHD, attentional bias.

Abbreviations

Electroencephalography (EEG), Typically Developing (TD), Attention-Deficit/Hyperactivity Disorder (ADHD), Wechsler Intelligence Scale for Children (WISC-III), Child Behavior Checklist (CBCL), Response Time (RT), Modulation Index (MI), Frontal Eye Fields (FEF).

1. Introduction

There is increasing evidence that the modulation of brain oscillations in the alpha band (8 – 12 Hz) plays an important role in the allocation of attention. Alpha modulation is thought to gate streams of information through the brain (Klimesch et al., 2007; Thut and Miniussi, 2009; Snyder and Foxe, 2010) as made specific in the 'alpha inhibition hypothesis' (Jensen and Mazaheri, 2010). The functional role of alpha band activity has particularly been studied in healthy adults using visuospatial covert attention paradigms (Worden, et al., 2000; Sauseng et al., 2005; Kelly et al. 2006; Thut et al., 2006, Händel et al. 2011; Bengson et al., 2012; ter Huurne et al., 2013). In most electroencephalography (EEG) and magnetoencephalography (MEG) investigations of covert spatial attention, a cue directs attention to the left or right visual hemifield, which allows for investigating alpha power changes in the hemispheres processing the attended and unattended visual hemifields. The key finding is that posterior alpha power increases ipsilateral and decreases contralateral to the attended visual hemifield, respectively inhibiting or facilitating the information flow (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006, Händel et al., 2011; Bengson et al., 2012; ter Huurne et al., 2013). High alpha power over task-irrelevant regions linked to the processing of the unattended information has proved to be of crucial importance for optimal suppression of distraction (Romei et al., 2010; Händel et al, 2011).

Typically developing (TD) children have been found to show a similar, adult-like pattern of alpha modulation during covert spatial attention (Vollebregt et al., 2015). The behavioral consequences, however, seem to be different than in adults; while previous results in adults showed that alpha modulation was associated with the ability to allocate attention (ter Huurne et al., 2013), this effect did not reproduce in children (Vollebregt et al., 2015).

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that is characterized by an inappropriate pattern of inattentiveness, hyperactivity and/or impulsivity causing impairment in multiple settings of life (American Psychiatric Association, 2013). A failure to modulate alpha activity might reflect ADHD, given the aforementioned tight links of alpha modulation with attention allocation in healthy adults. Furthermore, adults with ADHD demonstrated a problem in sustaining hemispheric alpha lateralization when cued to the left, resulting in an attentional bias in response times to the right visual hemifield compared to healthy adults (ter Huurne et al., 2013). Children with ADHD were also found to have a

response time bias towards the right visual hemifield in contrast to a leftward bias in TD children (8-14 years) (Chan et al., 2009). Younger TD children (5-9 years) however, showed a rightward bias (Takio et al., 2013). All in all, it is unclear whether children with ADHD would display deviant lateralized posterior alpha modulation with spatial covert attention similar to adults with ADHD and whether changes in their alpha power would relate to behavioral performance. A study investigating alpha modulation during a cross-modal attention task in children with ADHD showed that significant alpha modulation was absent in these children (Mazaheri et al., 2010). Also, alpha activity was relatively attenuated in ADHD compared to TD children during encoding of a working memory task (Lenartowicz et al., 2014). Alpha lateralization by modulating direction of attention was however not studied.

The aim of this study was to investigate alpha modulation in children with ADHD during a covert attentional task, and relate this to TD children and previous observations in adults with ADHD. We hypothesized that children with ADHD would lack a typical alpha modulation pattern and TD children would not. To this end, we compared the modulation of oscillatory brain activity of 7 to 10 year old TD children with children with ADHD as recorded by EEG while performing a visuospatial covert attention task.

2. Materials and methods

2.1 Participants

Data were acquired in the context of a clinical trial investigating alpha oscillations in children with and without ADHD (ClinicalTrials.gov identifier NCT01932398). The study was approved by the local Medical Ethics Committee (http://www.cmoregio-a-n.nl/) and conducted in accordance with the Declaration of Helsinki. All parents gave written informed consent; children gave verbal assent.

Children in the age range from 7 to 10 years old were recruited from primary schools in the area of Nijmegen, the Netherlands (TD children) and from referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, the Netherlands (children with ADHD).

The ADHD DSM-IV rating scale (American Psychiatric Association, 2000 [ADHD-RS-IV]) was filled out for both children with and without ADHD, only reaching the diagnostic cut off point in

the first group. It was filled out by parents to rate the current severity of ADHD symptoms. All nine attentional items, six hyperactive items and three impulsive items were rated. This was done using a 4-point Likert scale in which every item is scored as 0 (does never occur), 1 (occurs sometimes), 2 (occurs often) or 3 (occurs very often). For those children that used medication, symptoms were rated when based on time they were withdrawn from medication.

TD children were included if 1) they had never had a psychiatric, neurological, or cardiovascular disease or serious motor or perceptual handicap, 2) they did not score in the clinical range on the ADHD-RS-IV and any subscale of the Child Behavior Checklist (CBCL; Verhulst et al., 1996), both completed by parents, and 3) their estimated IQ was above 80. If an intelligence test had not taken place over the past two years, two subtests (i.e. Vocabulary and Block Design) of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991; Dutch version: de Kort et al., 2002) were administered to estimate full-scale intelligence. Validity coefficients for the Vocabulary and Block Design scores relative to all subtests scores are .88 for verbal IQ and .83 for performance IQ (Antshel et al., 2007).

Children with ADHD were included if they 1) had received a clinical diagnosis of ADHD according to DSM-IV, 2) scored in the clinical range on the ADHD-RS-IV, completed by parents, and 3) had an estimated IQ was above 80. They were allowed to take ADHD-related medication, but had to stop the medication no later than 12 hours prior to the experiment. The presence of clinical behavior on CBCL subscales other than the inattention subscale was discussed with the responsible clinicians to exclude the possibility of a comorbid diagnosis and verify that ADHD was the primary diagnosis in all cases. Data were collected between April 2012 and December 2014. Parents received reimbursement for travel costs and children received a present.

Initially, 34 TD children and 50 children with ADHD were interested in study participation and were examined on meeting inclusion criteria (*figure 1*). Two TD children did not meet inclusion criteria and two withdrew from participation. Five ADHD were not enrolled because they did not meet inclusion criteria, 14 withdrew from participation and one declined due to time constraints of the study. Thus, 60 children participated in this study (TD: N=30; ADHD: N=30). Seven data-sets from TD children were excluded for the following reasons: the child performed below chance-level (<50% correct) (N=1), there were technical problems (N=2), the quality of the EEG-data was deficient (N=1), the child used a different strategy resulting in insufficient correct responses on the invalid trials (for further information, see Vollebregt et al., 2015) (N=3), or

withdrew from participation (N=1). Six data-sets from children with ADHD were excluded for the following reasons: the child performed below chance-level (<50% correct) (N=1), there were technical problems (N=2), the quality of the EEG-data was deficient (N=2), the use of a different strategy resulting in insufficient correct responses on the invalid trials (N=1), or withdrew from participation (N=2). Finally, data from twenty-two TD children and twenty-two children with ADHD remained for analysis. However, since we did not counterbalance gender during recruitment, significantly more boys ended up in the ADHD group than in the TD group (TD: 41% boys, ADHD: 77% boys; p = .031, two-tailed Fisher's exact test). More importantly, the ADHD group contained only 5 girls. Previous literature has regularly pointed towards gender differences within ADHD. Gender differences within ADHD have for instance been found in attentional performance (Hasson and Fine, 2012), the functional neuroanatomy of working memory (Valera, Brown, Biederman et al., 2010), and resting state EEG (Dupuy et al., 2013; Dupuy et al., 2013). Due to this known influence of gender within ADHD and a large influence on the current results (see section 3.5), we decided to continue analyses with boys only. Therefore, our study will focus on the analysis of 9 TD boys and 17 boys with ADHD. Note that the sample of TD children is largely overlapping with the sample of another paper (Vollebregt et al., 2015).

>> Figure 1; single column 90 mm width <<

2.2 Study procedure

The task and data collection procedure were identical to that described in Vollebregt et al. (2015). Therefore large parts of the materials and methods section are identical. All measurements were performed at the Donders Centre for Cognitive Neuroimaging, Nijmegen, the Netherlands. Children and their parents visited the institute twice. First, if not available, intelligence was estimated and the Line Bisection Task (Schenkenberg et al., 1980; see section 2.3 for a description of this task) was performed. Furthermore, the first visit was used to explain and practice the visuospatial covert attention task, subsequently referred to as *the attention task*. This practice session was conducted while tracking the eyes to train the children to keep fixated at the center, but without EEG measurement. During the second visit the attention task was performed while tracking the eyes and recording the EEG. Medicated children with ADHD were not allowed to take their medication on the day of the EEG measurement and had to

perform the Line Bisection Task a second time during the second visit, this time off medication. In addition, two resting state EEG sessions, in which the child was instructed to sit quietly for 2 minutes with eyes open and 2 minutes with eyes closed, were recorded during the second visit. We do not report on the resting state data in this manuscript.

2.3 Line Bisection Task

The line-bisection task comprised 17 horizontal black lines of 2-mm width on an off-white sheet of paper (21 x 30 cm). The distance between the lines was 6 mm, except for the distance between the 11th and 12th line, which was 31 mm. The length of the lines ranged from 72 mm to 149 mm, with an average length of 112 mm. They were pseudo randomly positioned so that 5 lines appeared 50 mm from the left margin, 5 lines appeared 50 mm from the right margin and the other 7 lines appeared in the middle of the sheet. The left lateralized lines had lengths of 72, 101, 117, 141, 149 mm, with an average of 114 mm. The right lateralized lines had lengths of 88, 101, 119, 132, 147 mm with an average of 117 mm. The centered lines had lengths of 112, 134, 90, 103, 119, 72, 111 mm with an average of 106 mm. The sheet was laid in front of the child's midline. In a random half of the participants, the sheet was presented upside down, flipping left and right and creating the big distance between the 6th and 7th line. Next, the child was instructed to bisect the line in what he or she thought to be two parts of equal length. This was done with a ballpoint pen. Only one line was presented at a time, the others were covered with two blank off-white sheets of paper. All children performed the task with their right, preferred, hand without any time restrictions.

2.4 The attention task

Like in Vollebregt et al. (2015), an adjusted version of Posner's cueing paradigm for spatial orienting of attention was used (Posner, 1980), in which the goal was to save a fish from being eaten by a shark, with cartoon characters inspired by the film 'Finding Nemo'. For a figure of the task design, please see Vollebregt et al. (2015). The task was programmed and presented using the software package Presentation (Neurobehavioral Systems, Albany, CA). The task started with a 1-minute introduction video in which a shark recapped the most important instructions. Trials started with a pre-cue period (500 ms) with a shark presented at each side of the screen and a fish presented centrally. The child was instructed to fixate at the fish in the

middle of the screen throughout the task. The child was also instructed to sit as quietly as possible. Influences of movement on the eyetracker and EEG recordings were shown to the child in advance to illustrate the importance of sitting still. An attentional cue was presented in a 200 ms interval, in which the fish shifted gaze towards the left or the right shark indicating the side of the upcoming target if validly cued or indicating the opposite side if invalidly cued. In the next period (1000-1500 ms jittered) the child was expected to prepare for the upcoming target, hence this period was referred to as the *preparation period*. Next, the sharks both opened their mouths (100 ms), the target being the shark with the widest mouth. The child had to press the left or right button with the right index or middle finger to indicate the left or right shark, respectively. Correct responses had to be delivered within 1400 ms after target presentation to prevent negative feedback. Depending on the button press, positive or negative feedback was then presented for 500 ms, consisting of a happy fish or a fish bone, respectively. As encouragement a short task-related video with a shark was shown after every 37 trials.

During the first visit, the child practiced 100 trials (40 valid trials and 10 invalid trials per visual hemifield). Hence, the cue predicted the target location in 80% of the trials. During the second visit, the task consisted of 368 trials (138 valid trials and 46 invalid trials per visual hemifield). Hence, the cue predicted the target location in 75% of the trials. The correct prediction of the cue was set higher in the practice session to stimulate the child to use the cue information while learning the task. The left or right cue occurred with equal probability.

2.5 Eye tracking

Eye gaze was calibrated using a corneal reflection eye tracker and ClearView software (Tobii 1750, Tobii Technology Sweden), recording both eyes. Following a five point calibration procedure, the eyetracker made it possible to monitor fixation during the pre-cue and preparation period. During the pre-cue period, the cue was presented only when the child fixated on the screen center. If not fixating during the subsequent preparation period, three different types of instruction videos were presented immediately depending on the size of the deviation from the middle. It gave instruction to fixate on the eyes of the fish (small deviations), to fixate on the fish (median deviations), or to not look at the sharks (large deviations).

2.6 EEG recordings

The EEG was recorded from 32 scalp electrodes placed according to the 10-20 system using the Acticap and BrainAmp system (Brain Products GmbH, Munich). The vertex (electrode between Cz and Fz) was used as online reference; offline the data were referenced to the average of all electrodes. Electrode Fpz was used as ground. Electrode impedance was kept below 20 kOhm. The data were sampled at 500 Hz.

2.7 Analyses

Data were processed and analyzed using MATLAB 2012a (The MathWorks, Inc., Natrick, MA) and the FieldTrip analysis toolbox (http://fieldtrip.fcdonders.nl). Statistical analyses were also partly conducted employing the SPSS statistical program (SPSS 19.0). When correlation analyses were performed, these were always tested non-parametrically using a Spearman correlation test.

2.7.1 Behavioral performance

RTs faster than 100 ms were considered too short to reflect stimulus perception (Luce, 1986), while RTs larger than 4 times the standard deviation of the mean were regarded outliers (Schmiedek et al., 2007). These trials were therefore rejected from behavioral analyses. First, traditional hit-rate and RT analyses – defined as secondary outcome measures in the trial registration – were performed. To this end, percentage correct responses and mean RT and standard deviation were analyzed. However, RTs were expected to be distributed as an exponentially modified Gaussian (ex-Gaussian) distribution, implying that RTs contained a mean (mu) and standard deviation (sigma) of a Gaussian component and a mean (tau) of the exponential component (Lacouture and Cousineau, 2008). Children with ADHD are thought to have slower responses due to a larger tau in particular (Hervey et al., 2006).

2.7.2 Spectral analysis of the EEG data

Data segments showing artifacts such as muscle potentials, and amplifier or electrode noise, were identified using a semiautomatic routine and were excluded from further analyses. An independent component analysis was used to detect and remove component(s) with

electrooculographic origin, using a *fastica* algorithm (Hyvärinen, 1999). The EEG recordings were bandpass filtered at 2-30 Hz. Only trials in which the child fixated were used for further analysis. A fast Fourier transformation (FFT), using a sliding time-window being T = 5 cycles (T = 5/f) long was used to estimate the time-frequency representations of power (2-30 Hz in steps of every 2 Hz). The window was advanced in 50 ms increments. Prior to calculating the power using the FFT, the data in each window was multiplied with a Hanning taper. The time-frequency representations of power were calculated per trial and then averaged (Tallon-Baudry and Bertrand, 1999). This method allowed us to have optimal control of time and frequency smoothing. The time interval was cue-locked from -0.25 to 1.5 s with cue-onset at time 0 s. The alpha modulation index (MI) from cue-locked data – our primary outcome measure in the trial registration – was used to investigate whether a task-based modulation could be observed in the alpha band (8-12 Hz). The MI was computed by subtracting alpha power of right-cued trials from left-cued trials for each electrode. This subtraction was subsequently normalized by dividing by the mean of these two values:

$$MI = \frac{(alpha_{left\ cued\ trials} - alpha_{right\ cued\ trials})}{\frac{1}{2}\ (alpha_{left\ cued\ trials} + alpha_{right\ cued\ trials})}$$

Since alpha modulation has been observed in occipital and parietal regions in similar tasks (Worden et al., 2000; Thut et al., 2006; Vollebregt et al., 2015), we a prior selected occipital and parietal electrodes (except for the central electrodes Pz and Oz and the most lateral electrodes P7 and P8). The MI was averaged over left (left MI) and right (right MI) hemisphere parietal and occipital electrodes (left: P3, PO9, O1; right: P4, PO10, O2). From these values we constructed a combined MI (left MI minus right MI), which is equivalent to an index based on ipsilateral versus contralateral activity. The MI was computed was based on time-frequency representations of power, allowing us to quantify the MI as a function of time. For parts of the analyses, the MI was subsequently averaged over time.

A cluster based permutation test was performed for each group to identify time clusters for which the left MI differed significantly from right MI (van Ede et al., 2011). This test controls multiple comparisons by identifying significant clusters of time points rather than significant individual time points over the time-interval (-0.2 -1.5s).

3. Results

The visuospatial covert attention task was performed by the 9 boys without and 17 boys with ADHD. For a figure of the task design, please see Vollebregt et al. (2015). The fish in the middle cued the children to attend to the left or the right shark. After a preparation interval (1000-1500ms), both sharks opened their mouth and the children had to indicate by a button press which of the two sharks opened their mouth the widest. In 75% of the trials, the cued shark opened the mouth the widest, whereas in the remaining 25% trials the uncued shark did so.

3.1 Demographic and Clinical Characteristics

The demographic and clinical characteristics are summarized in Table 1. As expected based on the inclusion criteria, there was a significant difference between groups with respect to the ADHD rating (total t(23.309) = -15.816, $p < .001$, inattentive: t(19.681) = -10.895, $p < .001$, hyperactive/impulsive: t(21.568) = -16.911, $p < .001$, independent sample t-tests without the assumption of equal variance) and medication-use ($p = .002$, two-tailed Fisher's exact test). All children were right-handed. There was no difference between groups with respect to age or full-scale IQ. The ADHD group scored higher, and mostly significantly higher, on all problem behavior scales as measured with the CBCL, than the controls (see Table 1).

>> Table 1 <<

3.2 Task performance

The amount of aborted trials following deviation from fixation was larger in boys with ADHD than boys without (TD: 5 ± 6 trials, ADHD: 16 ± 10 trials; t(24) = -2.987, $p = .006$). Trials that were later rejected based on lack of fixation during the preparation interval was also higher in boys with ADHD than boys without (TD: 23 ± 34 trials, ADHD: 52 ± 29 trials; t(24) = -2.268, $p = .033$). Trials were also rejected due to artifacts in the EEG signal. After all rejections, the number of valid trials was equal in both groups (TD: 181 ± 33 trials, ADHD: 164 ± 43 trials; t(24) = 1.037, $p = .310$) as was the number of invalid trials (TD: 43 ± 8 trials, ADHD: 40 ± 11 trials; t(24) =0.620, $p = .541$). TD boys had significantly more outliers (2 ± 1 trials) than boys with ADHD (0 ± 0

trials), although very small in both groups (t(24) = 4.457, $p < .001$), and an equal number of premature responses close to zero (t(24)=0.459, $p = .650$). In sum, a similar amount of trials remained for analyses in both groups.

3.2.1 Performance measures

Behavioral performance measures between conditions within groups were compared using one-sample t-tests while a comparison between groups was tested using independent sample t-tests. Results can be found in Table 2. TD boys were significantly faster on invalid trials than boys with ADHD (TD: 580 ± 131 ms, ADHD: 686 ± 120 ms, t(24) = -2.065, $p = .050$). Within-subject standard deviation of the RTs was larger in boys with ADHD on valid (TD: 127 ± 25 ms, ADHD 176 ± 34 ms, t(24) = -3.906, $p = .001$) and invalid trials (TD: 116 ± 38 ms, ADHD: 167 ± 34 ms, t(24) = -3.497, $p = .002$). Both groups showed a cueing effect in mean RT (TD: 31 ± 29 ms. t(8) = -3.1253, $p = .0141$. ADHD: 50 ± 68 ms, t(16) = -2.996, $p = .009$) that did not differ between groups (t(24) = -0.794, $p = .433$). When we studied TD children in our previous study (Vollebregt et al., 2015), we used ex-Gaussian RT performance measures. We intended to use these measures in the current study as well. However, when comparing groups using ex-Gaussian measures, all above described differences disappeared. When comparing the skewness of the RT distributions, these did not differ between groups (t(24)=1.457, $p = .158$). In line with this lack of difference, but in contrast to our prior expectations, tau did not significantly differ between groups (valid trials; TD: 111 ± 53 ms, ADHD: 115 ± 58 ms. t(24) = -0.204, $p = .840$. Invalid trials; TD: 100 ± 53 ms, ADHD: 113 ± 59 ms. t(24) = -0.575, $p = .571$). We therefore decided to relate traditional RT performance measures to alpha modulation measures. No significant results differences within or between groups were found on hit-rate. In conclusion, both groups were influenced by the cue, but boys with ADHD varied more in their response times and were slower to respond to invalid trials.

3.2.2 Visual hemifield bias

No systematic group differences with respect to a visual hemifield bias were found. Both groups showed some minor differences between visual hemifields in favor of the right visual hemifield; TD boys showed a larger slowing when having to switch to a left target after being invalidly cued to the right hemifield than in the opposite direction (mean RT when invalidly cued to left: 566 ±

142 ms, mean RT when invalidly cued to right: 595 ± 121 ms, t(8) = -2.846, *p* = .022). Boys with ADHD also showed a larger slowing of responses when having to switch to a left target after being invalidly cued to the right hemifield than in the opposite direction (tau RT when invalidly cued to the left: 84 ± 67 ms, tau RT when invalidly cued to the right: 143 ± 75 ms, t(16) = -3.014, *p* = .008).

The Line Bisection Task also showed a rightward bias, as indicated by the positive average values in both groups (TD: 2.351 ± 2.263 mm, t(8) = 3.117, *p* = .014; ADHD: 4.148 ± 4.006 mm, t(16) = 4.270, *p* = .001) without a significant difference between groups (t(24) = -1.238, *p* = .228).

>> Table 2 <<

3.3 Lateralized alpha modulation.

To study hemispheric modulation of oscillations following the cue-initiated allocation of attention, we contrasted the spectral power for left versus right cues for each hemisphere separately and in combination. First we calculated the time-frequency representations of power for left cued minus right cued trials, normalized by their mean and averaged over a priori chosen left (O1, PO9, P3) and right (O2, PO10, P4) occipital and parietal electrodes. In TD boys, the alpha power decreased in electrodes contralateral to the cue (right electrodes) while it relatively increased in ipsilateral electrodes (left electrodes) (*figure 2a*). This modulation was absent in ADHD boys (*figure 2b*). To study the spatial distribution of the effect we next considered the topographical representations. For each group, data were averaged in the interval in which alpha modulation was reported in previous research (ter Huurne et al., 2013) (0.4-1.00 s), as well as in the alpha band (8 – 12 Hz). The topographic representations are shown for TD boys (*figure 2c*) and boys with ADHD (*figure 2d*). This confirmed that the modulation in the alpha band was strongest over occipital and parietal electrodes in TD boys but was not obvious in boys with ADHD.

To further study the time course we considered the modulation in the alpha band for the left and right hemisphere MI separately (*figure 3a and 3b; top panel*). By subtracting them we obtained the combined MI (*figure 3a and b, bottom panel*). A permutation test controlling for multiple comparisons over time verified that left and right MI in the alpha band significantly

differed from each other in the interval 0.5-0.75 s after cue-onset (p = .012) in TD boys. In boys with ADHD however, no robust power changes were observed in either hemisphere (*figure 3b, top panel*) or between hemispheres (*figure 3b, bottom panel*) and no significant time cluster was found.

The average modulation was also considered in the 8 – 12 Hz alpha band in the 0.4 – 1.0 s interval (based on ter Huurne, et al., 2013). Again, occipital and parietal electrodes were used. In this case, a significant difference between left and right was found for both groups (TD: t(8) = 3.284, p = .011; ADHD: t(16) = 2.481, p = .025), However, this difference was significantly larger in TD boys than in boys with ADHD (F(1,24) = 6.407, p = .018) (*figure 3c*). Such a difference was not found when analyzing the -0.2 – 0.0 s baseline time interval (F(1,24) = 0.956, p = .338). In sum, these results showed an alpha lateralization pattern in TD boys that was significantly smaller in boys with ADHD.

>> Figure 2; one and a half column 140 mm width <<

>> Figure 3; one and a half column 140 mm width <<

3.4 Lateralized alpha modulation vs behavior

Next, we asked whether the effects of the cue on behavior were related to the alpha MI. First of all, since the amount of aborted trials following deviation from fixation and the later rejected trials based on lack of fixation during the preparation interval was higher in boys with ADHD than boys without, we correlated these values to combined MI. This was done by relating the combined MI, averaged over the alpha frequency band (8 – 12 Hz) and the a priori selected time points (0.4 – 1.0 s), subsequently combined over electrodes (left minus right) to the ET trial-abortion and ET trial-rejection. This did not result in significant correlations (ET trial-abortion, TD boys: r = .378, p = .316, boys with ADHD: r = -.208, p = .422; ET trial-rejection, TD boys: r = .548, p = .126, boys with ADHD: r = -.214, p = .410). Next, we related combined MI to the cueing effect on hit-rate and mean RT. This also did not result in a significant relationship with the cueing effect on hit-rate (TD boys: r = -.150, p = .700, boys with ADHD: r = -.098, p = .708) or mean RT (TD boys: r = - .000, p = 1.00, boys with ADHD: r = .056, p = .830) for either

group. In conclusion, the alpha modulation measures were not related to behavioral performance across individuals in either group.

3.5 The influence of gender

The current paper only reported data from boys. This was decided because we only had 5 girls in the ADHD group and gender seemed to have a large influence on the results. We will report the results of the gender comparisons albeit this should be considered tentative due to the low number of girls. An ANOVA with combined alpha MI (averaged over the alpha frequency band [8-12 Hz], selected time points (0.4-1.00 s), and subsequently combined over electrodes [left minus right]) as dependent variable, group (ADHD vs no ADHD) and gender (boys vs girls) as independent variables, and total IQ – which significantly differed between genders within the ADHD group (boys: 113.529 ± 14.680, girls 98.000 ± 8.746, $t(20) = 2.228$, $p = .038$) – as covariate, showed a significant group*gender interaction ($F(4,39) = 13.907$, $p = .001$). When including both genders, significant time clusters for which hemispheres significantly differed from each other were found for both children with (t = 0.35 – 0.9 s, $p = .004$) and without ADHD (t = 0.45 – 1.00 s, $p = .004$). Furthermore, there was no difference between groups for MI averaged over the alpha frequency band (8 – 12 Hz), selected time points (0.4 – 1.00 s), and either left electrodes ($t(42) = 0.581$, $p = .565$), right electrodes ($t(42) = -0.123$, $p = .903$), or left minus right electrodes ($t(42) = 0.605$, $p = .548$). As such, in future research it would be highly interesting to quantify the gender difference using larger groups.

4. Discussion

The current study investigated the modulation of alpha band activity in 7-10 year old boys with and without ADHD performing a visuospatial covert attention task while EEG was recorded. We found that the alpha power (8-12 Hz) in typically developing (TD) boys decreased in the hemisphere contralateral to the attended hemifield, whereas it increased in the other hemisphere, in line with previous findings in adults. This pattern was however not found in boys with ADHD. Specifically, there was a significant difference between groups in the amount of alpha modulation in the difference between hemispheres (lateralization). With respect to behavioral performance, boys with ADHD were slower on invalid trials and more variable in their

response times in general than TD boys. However, a clear relationship between the amount of alpha modulation and behavioral responses, such as a cueing benefit in response time or hit-rate, was lacking in both groups.

The absence of alpha modulation in boys with ADHD is in line with previous research in adults showing deviant maintenance of hemispheric alpha lateralization when cued to the left, (ter Huurne et al., 2013). It is also in line with previous research in children showing significant alpha modulation in TD children during a cross modal attention task, but not in children with ADHD (Mazaheri et al., 2010), and children with ADHD showing attenuated alpha activity compared to TD children during encoding of a working memory task (Lenartowicz et al., 2014). Clear evidence for a stronger attentional bias to the right visual hemifield in ADHD than in controls, as found in adults (ter Huurne, et al., 2013), was however lacking. In our previous study (with an overlapping sample), TD children with a large cueing effect, in which lateralized alpha modulation was found to be less pronounced, had a significantly larger bias to the right visual hemifield than children with a small cueing effect (Vollebregt et al., 2015). However, despite less pronounced lateralized alpha modulation in children with ADHD, these children did not have a significantly larger cueing effect than children without ADHD. Thus, while earlier we established a clear relationship between a cueing benefit and alpha lateralization in healthy adults that was lacking in adults with ADHD. Now we found this relationship also lacking in both children with and without ADHD.

According to the current results, boys with ADHD seem to be unable to modulate alpha activity during covert attention. Why would this be the case? Alpha oscillations are thought to be under top-down control; they can be disrupted by applying transcranial magnetic stimulation to the contralateral frontal eye fields (FEF) (Capotosto et al., 2009; Marshall et al., 2015). The FEF in turn, is thought to be part of the dorsal frontoparietal network for top-down control of visual attention (Corbetta and Shulman, 2002) and under the influence of the dorsolateral prefrontal cortex (Munoz and Schall, 2004). Malfunctions at different levels of the dorsal frontoparietal network could result in deviant top-down control in individual nodes and/or in (functional) connectivity between the nodes. A meta-analysis investigating functional abnormalities in ADHD showed dysfunctions in the right dorsolateral prefrontal cortex, posterior basal ganglia, and parietal areas (Hart et al., 2013). Further evidence showed that saccade-suppression signals in the FEF and superior colliculi are disrupted in ADHD, possibly originating from the prefrontal cortex and/or the basal ganglia by a lack of voluntary control of endogenous fixation (Munoz et al., 2003). Note that significantly more trials were aborted and later rejected based on lack of

fixation during the preparation interval in boys with ADHD than boys without, but these rejections did not correlate with alpha modulation. In addition, malfunctioning functional connectivity between frontal attentional control brain systems and the visual cortex in ADHD seems to be supported by a lack of anti-correlation between frontal theta activity and posterior alpha activity on a trial-by-trial basis during a cross-modal attention task in children with ADHD (Mazaheri et al., 2010; Mazaheri et al., 2013).

What may cause these differences within the dorsal frontoparietal network is unclear. It has been acknowledged for decades that modifying the dopaminergic transmission can improve ADHD symptoms (Zametkin and Rapoport, 1987). Dopaminergic neurons seem to play a role in various cognitive processes, amongst others the allocation of attention (Nieloullon, 2002). Although the involvement of dopaminergic dysfunction has long been suspected, the exact nature of its influence on ADHD related behavior remains to be uncovered (Nieloullon, 2002). According to Vaidya and Gordon (2013), there is evidence in ADHD both for low dopamine suggesting a deficit in midbrain-striatal-prefrontal dopamine function and for high dopamine with higher midbrain dopamine synthesis. These findings do not contradict each other per se; one may act as a compensatory mechanism for the other (Vaidya and Gordon, 2013). Prefrontal dopamine D1 receptors are suggested to contribute to the control that FEF has on the visual cortex (Noudoost and Moore, 2011). Hence, they may have an important role in the dorsal frontoparietal network. The relationship between dopamine and alpha oscillations is – to our knowledge - unknown and could further help us understand the differences within the dorsal frontoparietal network.

The analyses of the current paper focused on boys only. ADHD has been shown to be 2.3 times more common in boys than in girls (Bauermeister et al., 2007). In our sample we only had 5 ADHD girls. Although we did find a significant interaction between group (ADHD vs no ADHD) and gender (boys vs girls) with respect to the difference in alpha modulation between hemispheres, in combination with the low number of girls in the ADHD group (N=5) this should be considered tentative. In line with previous research on gender differences in ADHD children (Hasson and Fine, 2012; Valera et al., 2010; Dupuy et al., 2013a, Dupuy et al., 2013b) and differences in the alpha band in TD children (Clarke et al., 2001), it would be of great interest to further investigate how the ability to modulate hemispheric alpha lateralization might be different in boys and girls.

5. Conclusions

In summary, we found that boys with ADHD did not modulate alpha oscillations during a covert attention task like typically developing boys did. A clear relationship between the amount of alpha modulation and behavioral responses was not found in either group. In future studies it would be important to identify the prefrontal and striatal regions that might explain the different ability in modulating the alpha band activity. The top-down control influence of frontal structures and its relation to dopaminergic pathways should also be subject to further investigation. Computational modeling approached and co-registration of EEG and functional Magnetic Resonance Imaging might help to understand the frontoparietal network. Also, genetic information on dopamine could provide more information. Future research should therefore elucidate this different alpha modulation pattern closer by over-recruiting girls with ADHD and more systematically examine gender effects. There is also a need for more systematic studies of the effect of age on alpha modulation by comparing children, adolescents and adults with ADHD cross-sectionally in the same design and/or by conducting prospective longitudinal studies in children with ADHD. Furthermore, it would be interesting to explore if the aberrant modulation of the alpha band activity is different in different subtypes of ADHD. Such an approach could in the future help diagnosing ADHD subtypes. All in all, this study provides insight into the deviant nature of posterior lateralized alpha modulation, possibly as part of the dorsal frontoparietal network, during covert attention in ADHD. Further understanding the nature of malfunctioning in the dorsal frontoparietal network may eventually help to develop clearly focused treatment of the disorder. Promising with respect to the development of such treatment is the finding that alpha lateralization neurofeedback training has been shown to be superior to sham neurofeedback in healthy adults (Okazaki et al., 2015), demonstrating that these oscillations are trainable.

Conflict of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Buitelaar has been for the past years a consultant to, member of the advisory board of, and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myers Squibb, Schering-Plough, UCB, Shire, Novartis, and Servier. He is neither an employee of nor a shareholder in any of these companies. He receives no other financial or material support, including expert testimony, patents, and royalties. The other authors have no conflict of interest to report.

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Tables

Table 1. Demographic characteristics.

	Typically developing boys (N=9)	**Boys with ADHD (N=17)**	***p*-value**
Age, mean (sd)	8.46 (1.38)	9.15 (1.06)	*ns*
(Estimated) full-scale IQ, mean (sd)	121.44 (18.17)	113.53 (14.68)	*ns*
Medication for ADHD, N (%), mean intake in mg (sd)			≤ .01[a]
methylphenidate	0	10 (59), 34.00 (25.68)	
dexamphetamine	0	1 (6), 22.50 (0)	
no medication	9 (100)	6 (35)	
ADHD-RS-IV parent-rated, mean (sd)			
total symptoms	4.56 (2.40)	36.94 (7.17)	≤ .001
inattention symptoms	2.44 (1.67)	19.94 (3.94)	≤ .001
hyperactivity/impulsivity symptoms	2.11 (1.36)	16.88 (5.27)	≤ .001
CBCL (clinical cut-off boys), mean (sd)			
anxious/depressed (≥11)	2.78 (2.54)	4.24 (3.96)	*ns*
withdrawn/depressed (≥6)	1.22 (1.30)	2.59 (2.90)	*ns*
somatic complaints (≥7)	0.89 (1.17)	2.18 (2.46)	*ns*
social problems (≥10)	1.78 (1.56)	4.76 (3.75)	≤ .05
thought problems (≥7)	1.67 (1.73)	3.94 (2.95)	≤ .05
attention problems (≥13)	2.56 (2.24)	10.76 (2.08)	≤ .001
rule breaking behavior (≥7)	0.89 (1.17)	1.59 (1.37)	*ns*
aggressive behavior (≥17)	2.11 (1.96)	9.12 (4.74)	≤ .001
other problems	2.22 (1.56)	5.82 (1.98)	≤ .001

[a] Fisher exact test rather than independent sample T-test.

Table 2. Task performance.

Task performance	Typically developing boys (N=9)[a]	Boys with ADHD (N=17)[a]	*p*-value[b]
Hit-rate valid	92.70 ± 11.04	86.02 ± 7.08	*ns*
Hit-rate invalid	87.22 ± 20.03	77.49 ± 21.53	*ns*
Hit-rate cueing	5.48 ± 9.23	8.53 ± 19.30	*ns*
Mean RT valid	550 ± 131	639 ± 148	*ns*
Std RT valid	127 ± 25	176 ± 34	**≤ .001**
Mean RT invalid	580 ± 131	686 ± 120	**≤ .05**
Std RT invalid	116 ± 38	167 ± 34	**≤ .01**
Mean RT cueing	**31 ± 29***	**50 ± 68****	*ns*
Std RT cueing	-10 ± 25	-9 ± 26	*ns*

[a] within group differences between valid and invalid trials are indicated with stars (* $p \leq .05$, ** $p \leq .01$).

[b] *p*-value of independent sample t-test

Figure Legends

Figure 1. Consort flow diagram

Figure 2. The modulation of alpha band power in response to the spatial cue for TD (left column) and boys with ADHD (right column). (a) Time-frequency representation of the normalized MI (left minus right cues) for left (top panels) and right (bottom panels) occipital and parietal electrodes. The MI in the alpha range was postive in left electrodes and negative in right electrodes; i.e. alpha power decreased contralateral to the cue hemifield and increased ipsilaterally. (b) The modulation of alpha lateralization was absent in boys with ADHD (the line at t = 1.2 s represents first possible target onset and the subsequent grey area the jittered possible onsets of the target presentation). *c and d.* Topographic representation of the MI averaged over children, in the alpha band (t = 0.4 – 1.0 s). The alpha power clearly lateralized over posterior regions in TD boys, but not in boys with ADHD.

Figure 3. (*a and b*) Time course of the left and right MI, averaged over participants for the 8-12 Hz alpha band occipital and parietal electrodes (top panel). The time course of the combined MI (left electrode MI minus right electrode MI) (bottom pannels). The dashed square indicates the time cluster for which the MI in left electrodes and right electrodes differed significantly from each other in typically developing boys (t = 0.5-0.75; $p = .012$). (*c*) Modulation in the alpha band (t = 0.4 – 1.0 s; left and right occipital and parietal electrodes) demonstrating a significant difference between left and right for both groups (TD: $t(8) = 3.284$, $p = .011$; ADHD: $t(16) = 2.481$, $p = .025$), This difference was however significantly larger in TD children than in children with ADHD ($F(1,24) = 6.407$, $p = .018$).

Figure 1

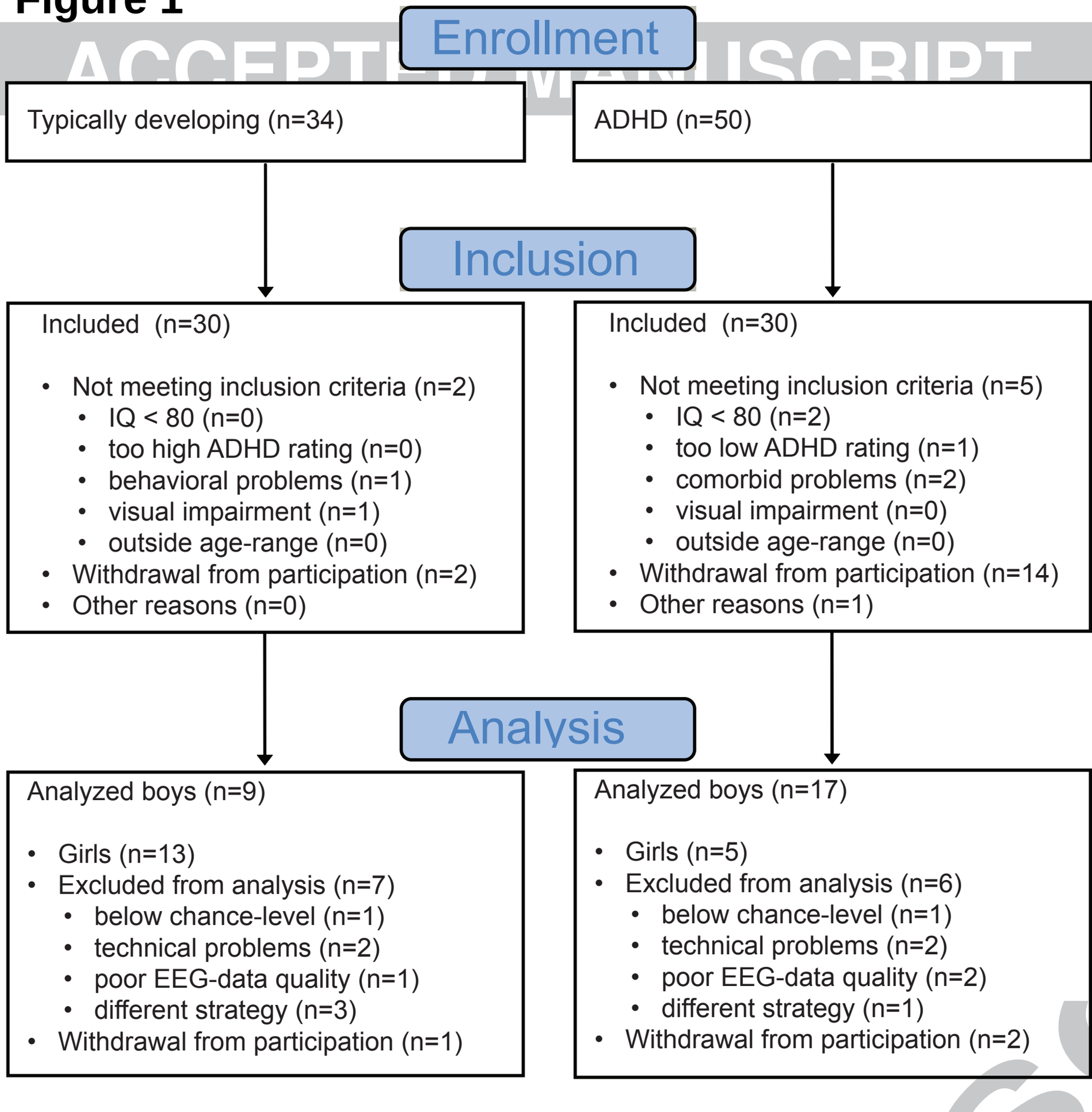

Figure 2

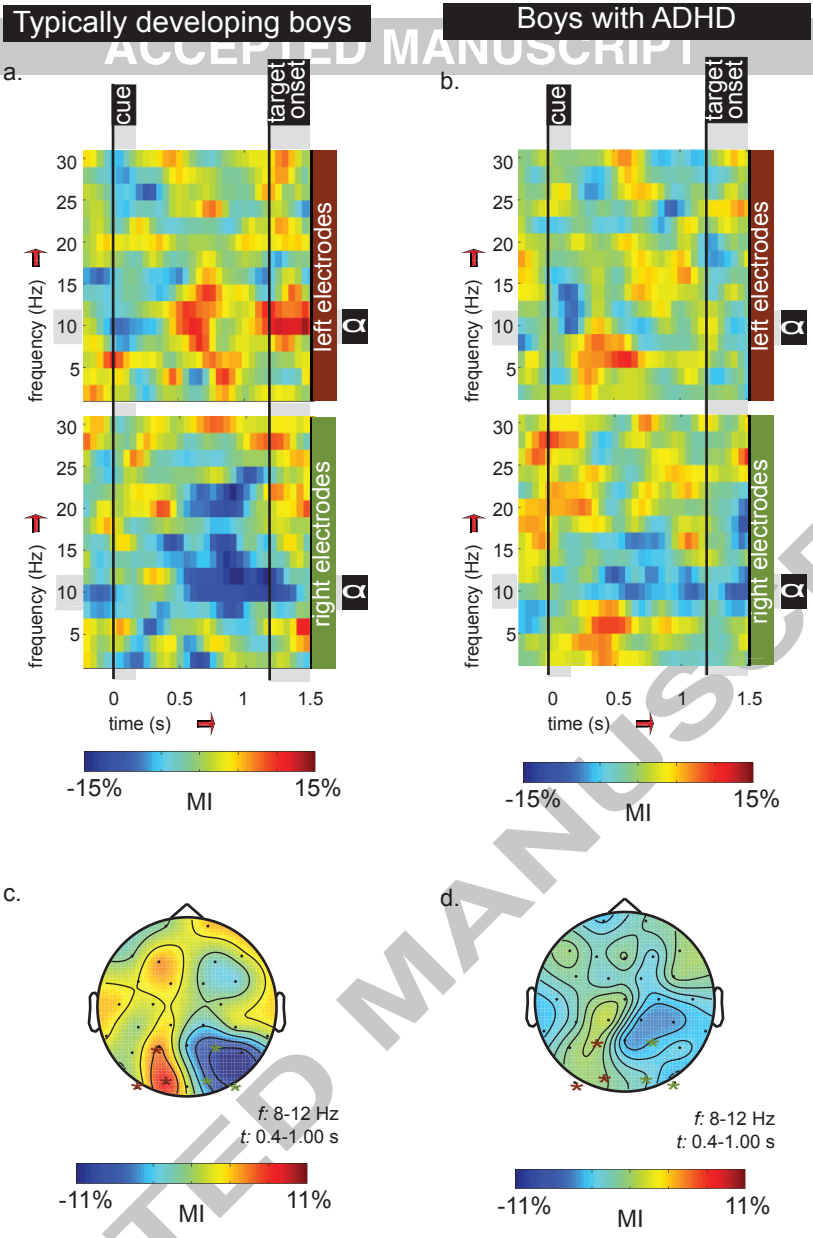

Figure 3